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Features of Anaphylactic Shock as the Most Severe Form of Anaphylaxis

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Abstract

Anaphylactic shock is involved in Type I Hypersensitivity Reaction.

Anaphylactic Shock is Anaphylaxis and Anaphylaxis is the most severe clinical manifestation of acute systemic allergic reactions. The rationale of this updated position document is the need to keep guidance aligned with the current state of the art of knowledge in anaphylaxis management. Special focus has been placed on regions in which national guidelines are lacking. All aspects have been assessed based on scientific evidence supporting statements. This guidance adopts the major indications from the previous anaphylaxis guidelines of the World Allergy Organization (WAO) and incorporates some slight changes in specific aspects such as the diagnostic criteria. Anaphylaxis is a severe, systemic hypersensitivity reaction that is rapid in onset and characterized by life-threatening airway, breathing, and/or circulatory problems, and that is usually associated with skin and mucosal changes. Because it can be triggered in some people by minute amounts of antigen (e.g. certain foods or single insect stings), anaphylaxis can be considered the most aberrant example of an imbalance between the cost and benefit of an immune response. This review will describe current understanding of the immunopathogenesis and pathophysiology of anaphylaxis, focusing on the roles of Ig E and IgG antibodies, immune effector cells, and mediators thought to contribute to examples of the disorder. Evidence from studies of anaphylaxis in humans will be discussed, as well as insights gained from analyses of animal models, including mice genetically deficient in the antibodies, antibody receptors, effector cells, or mediators implicated in anaphylaxis, and mice which have been "humanized" for some of these elements. We also will review possible host factors which may influence the occurrence or severity of anaphylaxis. Finally, we will speculate about anaphylaxis from an evolutionary perspective, and argue that, in the context of severe envenomation by arthropods or reptiles, anaphylaxis may even provide a survival advantage.

Keywords: Anaphylactic Shock, Anaphylaxis, Histamine, IgG, Ig E, Basophils, Cysteinyl Leukotrienes, Epinephrine, Food Allergy, Histamine, Ig E, Mast Cells, Platelet Activating Factor, Urticaria

Background

The WAO (World allergy organization) Anaphylaxis Committee has proposed the following definition for anaphylaxis:

"Anaphylaxis is a serious systemic hypersensitivity reaction that is usually rapid in onset and can cause death. Severe anaphylaxis is characterized by potentially life-threatening compromise of the airways, breathing and/or circulation, and may occur without the presence of typical features of skin or circulatory shock."

Recent publications show a global incidence of anaphylaxis between 50 and 112 episodes per 100,000 person-years while the estimated lifetime prevalence is 0.3-5.1%, variations depending on the definitions used, study methodology and geographic areas.

Population-based studies have estimated the incidence rate of anaphylaxis in the United States, the United Kingdom, and other developed countries to be in the range of 40 to 500 per million person-years.6 Lifetime prevalence estimates range from 0.05 % to 2% and appears to be increasing 3,6,8. Estimates of mortality associated with anaphylaxis have been between 0.5 and 5.5 per million population, with death reported to occur in 0.65% to 2% of patients. who experience severe anaphylactic reactions

(World Allergy Organ J. 2020 Oct; 13(10): 100472.Published online 2020 Oct 30. doi: 10.1016/j.waojou.2020.100472).

In Albania, there are no accurate statistics on allergies and anaphylaxis. However, a specific overview will be given through this Article, guided by world statistics.

Causes

Anaphylaxis is a severe allergic reaction that can progress to a life-threatening condition. It is caused by exposure to something you are allergic to. Symptoms involve multiple body systems including the skin, heart, stomach and respiratory tract. Between 1.6% and 5.1% of people in the United States have experienced at least one episode of anaphylaxis. The most common triggers are certain foods, certain medications, and insect bites. Anaphylaxis occurs in 1 in 50 people with allergies. Anaphylaxis is an allergy emergency that can cause death in less than 15 minutes. Epinephrine is the only drug that can reverse the symptoms. It is essential to use epinephrine first and epinephrine quickly. Then seek immediate treatment at your nearest emergency room.

Anaphylaxis occurs when symptoms affect two or more body systems. It is caused by your immune system flooding your body with chemicals to fight an allergen. These chemicals often work quickly to cause a cascade of allergy symptoms. Common causes of anaphylaxis are usually caused by a reaction to one of the following factors: the food insect poison treatment Latex vaccines (in rare cases), including anaphylaxis to COVID 19 vaccines.

While any allergen can cause a severe allergic reaction, certain foods, medications, and insect venom account for 90% of anaphylactic reactions.

- Legumes (such as peanuts)
- Animal proteins (such as cow's milk, eggs, finned fish and shellfish)
- Poison from stinging insects (such as bee stings, wasps, and yellow jackets)
- Poison from insect bites (such as fire ants)
- Pain medications (such as aspirin or ibuprofen)
- Tree nuts (such as almonds, walnuts, walnuts, and hazelnuts), soybeans, wheat, and sesame are other common triggers. Food allergy research reveals that more than 170 different foods can cause allergic reactions.

Antibiotics such as penicillin and amoxicillin are also common triggers. In rare cases, exposure to latex can also cause symptoms. How soon can it happen? Most anaphylactic reactions begin within minutes of exposure to an allergen. However, in some cases the response may take half an hour or more [1-3].

Factors That Can Increase the Severity of Anaphylaxis

Endogenous	Exogenous
sex, age	medication
cardiovascular disease	physical activity
mastocytosis	psychological burden
atopic disease	certain elicitors
elevated tryptase	sleep deprivation
ongoing infection	

Symptoms

Symptoms of anaphylaxis appear suddenly and can progress rapidly within minutes.

The sooner the severe symptoms start, the less chance the patient has to stay alive. The later symptoms appear, the more likely the patient will survive.

It is therefore imperative to start treatment with Adrenaline quickly.

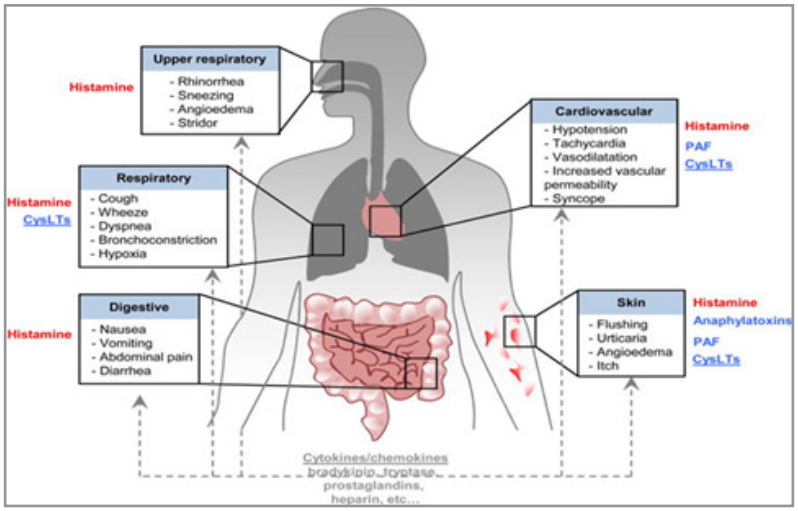
Early symptoms may be mild, such as a runny nose, skin rash or a "weird feeling". These symptoms can quickly lead to more serious problems, including:

- Problems with breathing
- Hives or swelling
- Throat tightness
- Hoarse voice
- nausea
- Vomiting
- Abdominal pain
- diarrhea
- Dizziness
- Fainting
- Low blood pressure
- Rapid heartbeat
- Feeling of punishment Cardiac arrest

People who have had a severe allergic reaction are at risk for future reactions. Even if your first reaction is mild, future reactions may be more severe. This is why it is important to carry self-injectable epinephrine if you are in danger and call 911 in case of a very serious reaction. The best way to understand anaphylaxis and the things that can cause this severe allergic reaction is to see an allergist who will help you manage your condition.

Difficulty in breathing, wheezing or airway obstruction Rapid and weak pulse, low blood pressure or abnormal heart rhythm Severe swelling, including swelling of the mouth, throat and airways Feeling dizzy or faint Loss of consciousness Sudden drop in blood pressure, cardiac or respiratory arrest [4-8]

Tables of Symptoms by Organs



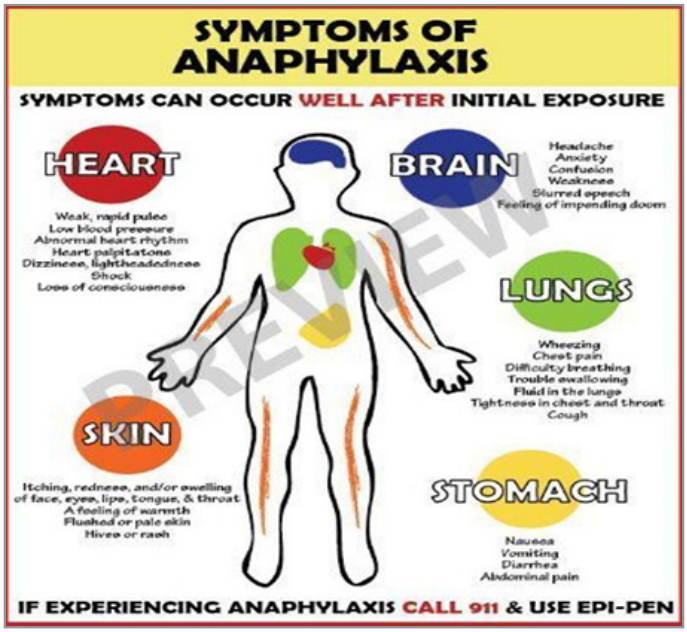
Anaphylaxis Severity Grades are as Follows According to the WAO System
(World Allergy Organization)

The World Allergy Organization (WAO) guidelines for anaphylaxis were published in 2011 and the current guideline adopts their main indications, including some new changes. Intramuscular epinephrine (adrenaline) continues to be the first-line treatment for anaphylaxis. However, its use remains suboptimal. After the occurrence of anaphylaxis, patients should be referred to a specialist to evaluate the possible cause and to be educated on recurrence prevention and self-management. The limited availability of epinephrine auto-injectors remains a major problem in many countries, as does their affordability for some patients.

In this classification, only some grades 3 or 4-5 would be consistent with the definition of anaphylaxis, while grades 1-2 constitute non-anaphylaxis. Some additional symptoms, such as drooling or neurological symptoms, may be applicable in the pediatric setting111. The potential for severity of reactions to change should be recognized [9-12].

WAO systemic allergic reaction grading system.

(Not anaphylaxis)		ANAPHYLAXIS		
Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Symptom(s)/sign(s) from 1 organ system present	Symptom(s)/sign(s) from ≥2 organ	Lower airway	Lower airway	Lower or upper airway
Cutaneous		Mild bronchospasm, eg, cough, wheezing, shortness of breath which responds to treatment	Severe bronchospasm eg, not responding or worsening in spite of treatment	Respiratory failure and/or
Urticaria and/or erythema-warmth and/or pruritus, other than localized at the injection site		And/or	And/or	Cardiovascular
And/or		Gastrointestinal	Upper airway	Collapse/hypotension
Tingling, or itching of the lips* or Angioedema (not laryngeal)+		Abdominal cramps+ and/or vomiting/diarrhea	Laryngeal edema with stridor	And/or
Or Upper respiratory		Other	Any symptom(s)/sign(s) from grades 1 or 3 would be included	Loss of consciousness (vasovagal excluded)
Nasal symptoms (eg, sneezing, rhinorrhea, nasal pruritus, and/or nasal congestion)		Uterine cramps		Any symptom(s)/sign(s) from grades 1, 3, or 4 would be included
And/or		Any symptom(s)/sign(s) from grade 1 would be included		
Throat-clearing (itchy throat)*				
And/or				
Cough not related to bronchospasm				
Or Conjunctival				
Erythema, pruritus, or tearing				
Or Other				
Nausea				
Metallic taste				



Phys-Pathology of Anaphylactic Shock

The "Recent International Consensus on (ICON) Anaphylaxis" described anaphylaxis as "a serious, generalized or systemic allergic or hypersensitivity reaction that may be life-threatening or fatal." Multiple potential pathways in antibody-mediated anaphylaxis are ultimately Antigen-Antibody collision. Anaphylactic shock as severe anaphylaxis by classification belongs to the Distributive Shock group in which there are four important physio-pathological and clinical elements

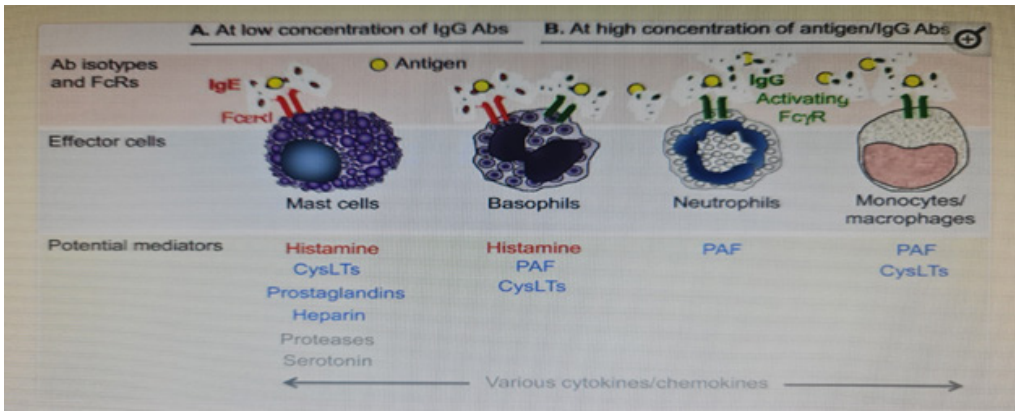
- Acute hypoxia
- Acute Hypotension
- Metabolic acidosis
- Paralytic vasodilatation of blood capillaries (as a result of the release of enzymes in the blood such as Histamine and other inflammatory mediators).

If evaluated carefully, these features can be observed.

The Roles of Different Antibodies, Effector Cells and Mediators in Anaphylaxis in Humans.

Antigen-specific IgE antibodies and FcεRI-bearing effector cells (eg, mast cells, basophils) play a dominant role in anaphylaxis induced (sometimes by very small amounts of antigen) when IgG antibody concentrations are low. eg, human mast cells are thought to produce little or no serotonin), Mast cells and basophils produce Histamine, neutrophils produce Platelet Activating Factor. IgE - IgE antibodies can undeniably play an important role in conferring the immunological specificity of effector cell activation in anaphylaxis and other allergic diseases.

In healthy individuals versus ~10 mg/ml for IgG)15; however, IgE can be found at much higher levels in individuals with allergic disease. IgE binds to the high-affinity receptor, FcεRI, on the surface of blood basophils and tissue-resident mast cells, and other cell types, including neutrophils, eosinophils, monocytes and dendritic cells, and platelets. After exposure to a bivalent or multivalent allergen, cross-linking of FcεRI-linked IgE causes the activation of mast cells and basophils and the immediate release of preformed mediators such as histamine and various proteases, as well as the de novo synthesis of many inflammatory mediators. such as some leukotrienes, prostaglandins and cytokines.



Note: Ab isotypes are Antibodies.

- **FcR:** Receptor with a Crystallizable Fragment I that Ensures that Each Ab Produces an Immune Response Against a Specific Ag
- **CysLTs:** Cysteinyl Leukotrienes are Mediators of Inflammation
- **PAF:** Platelet Activation Factor

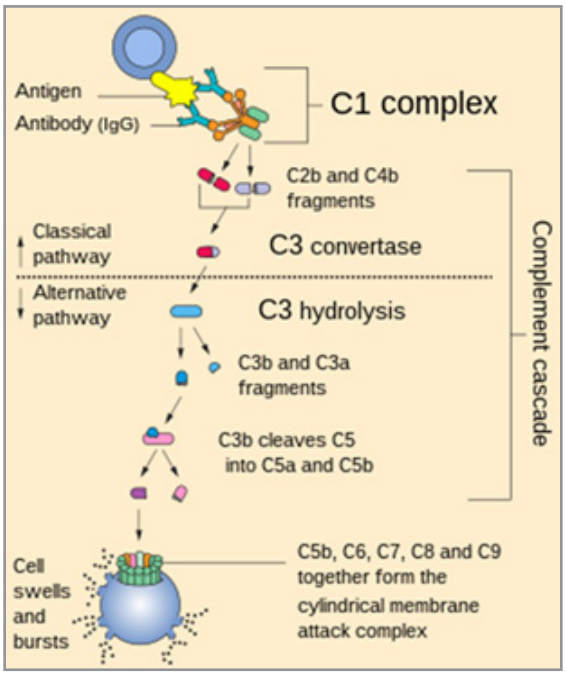
Several studies have concluded that the use of the therapeutic anti-IgE antibody omalizumab as adjunctive treatment during food or venom immunotherapies may reduce the risk of severe allergic reactions, including anaphylaxis, and some but not all trials have also reported that improves speed. and the efficacy of immunotherapy in achieving desensitization (The pathophysiology of anaphylaxis - PMC (nih.gov) [13-34].

Role of IgG and FcγRs

In addition to IgE, we now know that mouse IgG can also cause passive systemic anaphylaxis (PSA) reactions, with physiological manifestations similar to those seen in IgE-dependent PSA (mainly hypothermia, vasodilation and cardiopulmonary changes)50-60. Whether IgG antibodies also mediate anaphylaxis in humans remains to be proven and is the subject of a recent review 2. As shown in mice, IgG-mediated anaphylaxis usually requires a very high dose greater antigen exposure than IgE-mediated anaphylaxis 61, and systemic anaphylaxis also requires systemic absorption of ingested antigen62. Such conditions may be encountered in the case of anaphylaxis occurring in response to the infusion of large amounts of a drug or a therapeutic monoclonal antibody (mAb) [35-47].

Role of Complement

Activation of the complement cascade occurs in response to many stimuli and leads to the generation of small polypeptides: C3a, C4a and C5a, also called anaphylatoxins, which are potent inflammatory mediators. Ample evidence suggests that anaphylatoxins can be involved in anaphylaxis. Decreased levels of complement and production of C3a and C5a are observed in human anaphylaxis. Anaphylatoxins can activate various myeloid cells, including mast cells and basophils. Injection of low doses of C3a, C4a, or C5a into the skin of healthy volunteers causes immediate stinging and flaring reactions. In addition, one study showed that blood levels of C3a, C4a, and C5a correlated with the severity of anaphylaxis in humans [48-52].



Mast Cells

Mast cells are seen as key players in IgE-dependent allergy and anaphylaxis.16, 70 Mast cells typically express large numbers of the high-affinity IgE receptor, FcεRI. During IgE-dependent immune responses, antigen-dependent cross-linking of antigen-specific IgE bound to FcεRI causes aggregation of FcεRI, triggering the activation of downstream signaling events that lead to the secretion of several biologically active products thought to be implicated in allergic reactions, such as histamine and various cysteinyl leukotrienes (Cys-LTs). Additional evidence for the role of mast cells in anaphylaxis comes from the observation that patients suffering from mastocytosis, a disease characterized by the presence of large numbers of mast cells in various organs,84 have a high incidence of anaphylaxis.85 In children with mastocytosis . Elevated serum tryptase levels, used as an indicator of mast cell burden, is a risk factor for anaphylaxis and for the severity of anaphylaxis episodes [53-67].

Basophils

Human basophils also express high levels of the high-affinity IgE receptor FcεRI 94 and express the activating IgG receptor FcγRIIA and the inhibitory IgG receptor FcγRIIB 95. Several lines of evidence suggest that basophils participate in anaphylaxis. For example, IgE-dependent activation of human basophils is associated with elevated levels of several basophil cell surface markers, such as CD203c or CD63, and this forms the basis of "basophil activation assays" that can be used to to diagnose or confirm allergen sensitization and to monitor the effects of attempts to treat these conditions with immunotherapy [68-71].

Monocytes/Macrophages

Monocytes and macrophages express high levels of activating FcγRs, and can also respond to anaphylatoxins. These data suggest that monocytes/macrophages may play an important role in anaphylaxis. However, to our knowledge, the extent to which monocytes/macrophages may contribute to anaphylaxis in humans has not yet been determined [72-77].

Neutrophils

The possible functions of neutrophils in anaphylaxis have recently been reviewed in detail. Human neutrophils express several activating FcγRs, can produce histamine, and can release platelet-activating factor (PAF. In addition, human neutrophils are said to express FcεRI, especially in some patients with asthma. The major enzyme conserved in neutrophils is myeloperoxidase (MPO). A recent report shows that circulating MPO levels are increased in patients with anaphylaxis compared to healthy donors [78-81].

Platelets

Anaphylaxis in humans is associated with platelet activation, presumably in response to PAF and/or other mechanisms, and activated platelets may release mediators, such as platelet factor 4 (PF4) and serotonin, that may contribute to the pathophysiology of anaphylaxis. Furthermore, human platelets can express FcεRI, FcεRII, and FcγRIIA, and platelets can be activated ex vivo following incubation with serum from allergic patients and subsequent exposure to the relevant allergen. Two recent reports have shown that, in basophil activation assays performed on ex vivo blood specimens, basophils (a potential source of PAF) can form bonds with platelets, identifying this interaction as one that warrants further investigation in the context of anaphylaxis [82-87].

Histamine

Histamine has long been considered an important mediator of anaphylaxis. Woodrow and colleagues showed that aerosol administration of histamine caused bronchoconstriction in healthy volunteers, although the effect of histamine was much less potent than that of leukotrienes (see Leukotrienes, below). Intravenous administration of histamine in volunteers can reproduce the symptoms of anaphylaxis, including skin rash, headache, airway obstruction and transient hemodynamic changes, mainly represented by systemic hypotension, tachycardia and increased left ventricular performance.

There are four known histamine receptors, called H1-4. Studies using the receptors suggest that some of the systemic effects of histamine, including airway obstruction and tachycardia, are mediated primarily through the H1R, while others, including flushing and headaches, appear to be mediated by both receptors. H1 and H2. H1 antihistamines (Benadryl) are commonly used as adjunctive treatment for acute anaphylaxis and anaphylactoid reactions. Mast cells and basophils likely represent the main sources of histamine in anaphylaxis [88-96].

Bradykinin

Mast cells produce Bradykinin. It is hypothesized that bradykinin plays a protective role in cardiac anaphylaxis by accumulating on the luminal surface of the coronary endothelium and inducing, in an autocrine manner, a B2 receptor-mediated production of nitric oxide and prostacyclin at concentrations sufficient to cause a paracrine effect in coronary. Activation of the kinin-bradykinin system is particularly important in the regulation of blood pressure and in inflammatory reactions, through the ability of bradykinin to increase vascular permeability and cause vasodilation in some arteries and veins. Bradykinin caused a dose-related increase in vascular resistance. Because bradykinin is generally a vasodilator, we investigated the possibility that bradykinin-induced vasoconstriction was due to interactions with other suppressor systems. The Kinin-Bradykinin System Indirectly Affects Anaphylaxis (Bradykinin - Wikipedia).

The Inflammatory Cytokine, Tumor Necrosis Factor-α (TNF-α) Is released as a preformed mediator, and also as a late phase mediator with other cytokines and chemokines. Many of these mediators are believed to be responsible for the pathophysiology of anaphylaxis (Death by TNF: a road to inflammation | Nature Reviews Immunology).

Platelet-Activating Factor (PAF)

PAF is a potent phospholipid-derived mediator implicated in platelet aggregation and is thought to play an important role in a variety of immune and inflammatory responses. The biology of PAF and its potential role in anaphylaxis have recently been reviewed in detail. PAF can be released from a variety of human cells, including purified lung mast cells and blood basophils after ex vivo stimulation with anti-IgE antibodies, and from purified neutrophils after in vitro incubation with heat-aggregated human IgG. Many of the cell populations that produce PAF can also respond to PAF, including platelets, mast cells, neutrophils, and macrophages.

Injection of PAF into the skin of healthy volunteers causes stinging and burning reactions. Since these reactions could be blocked by H1-antihistamines, it was initially proposed that PAF induces wheals through secondary release of histamine from cutaneous mast cells. However, unlike human lung mast cells and peripheral blood-derived mast cells, cutaneous mast cells do not degranulate in response to PAF stimulation ex vivo. In addition, Krause and colleagues showed that intradermal injection of PAF, unlike histamine and codeine, did not cause a statistically significant increase in dermal histamine levels in healthy volunteers. A limited number of reports have assessed concentrations of PAF or PAF-acetylhydrolase (PAF-AH)—an enzyme responsible for the rapid degradation of PAF—after anaphylaxis in humans. In these reports, circulating PAF levels were increased and circulating PAF-AH activity was inversely correlated with the severity of anaphylaxis [97-106].

Cysteinyl Leukotrienes (CysLTs)

A third class of potential mediators of anaphylaxis was originally called "slow-reacting anaphylaxis substance" (SRS-A) and consists of three bioactive cysteinyl leukotrienes (CysLTs): leukotriene B4 (LTB4), LTC4 and LTD4. CysLTs are synthesized from arachidonic acid by a variety of cells, including mast cells, basophils, and macrophages.130 CysLTs and their metabolites can be measured by mass spectrometry, and some reports indicate that the levels of some of these products, namely LTE4, 2,3 -dinor-9α,11β-PGF2 and 9α,11β-PGF2 increase during the onset of anaphylaxis. While these reports indicate that CysLT and their metabolites may be good biomarkers of anaphylaxis, they do not

prove that these compounds make a significant contribution to the clinical manifestations of anaphylaxis. However, several observations suggest that CysLTs can induce acute allergic reactions. When injected intradermally into healthy volunteers, each of the three CysLTs elicited a scratch and flare reaction 134. In addition, aerosol administration of LTC4 and LTD4 to healthy subjects induced bronchoconstriction 1000 times more potent than histamine [107-112].

Other Potential Mediators

Anaphylaxis causes changes in the levels of many other mediators that can potentially contribute (positively or negatively) to clinical signs and symptoms. This includes tryptase, prostaglandins and cytokines/chemokines. Depletion of the precursor of bradykinin, the high-molecular-weight kininogen, has been observed in anaphylaxis, likely through activation of the plasma and kallikrein systems. Patients with anaphylaxis may also experience depletion of coagulation factors, including Factors V and VIII, and in extreme cases develop diffuse intravascular coagulation.

While most patients treated promptly for anaphylaxis recover without apparent sequelae, some develop recurrent signs and symptoms that require continued treatment with epinephrine and for which corticosteroids are administered. Such consequences are thought to reflect the "late" consequences of some of the mediators released by the effectors of anaphylaxis, such as cysteinyl leukotrienes, cytokines and chemokines, or by structural cells activated in this environment. Finally, mast cells can release adenosine after the activation of dependent on IgE and adenosine may have complex effects, mediated through different adenosine receptors with distinct functions, which have the potential to influence the pathophysiology of anaphylaxis. However, more work is needed to determine the importance of most of these mediators in anaphylaxis, particularly in humans [113-121].

Genetic Diversity/Host Factors Affecting Anaphylaxis

Genetic modifiers can influence mast cell activation and the development of anaphylaxis, as shown in the differences observed between 129/Sv and C57BL/6 strains of mice. Ethnic differences in rates of food allergy and anaphylaxis suggest that genetic modifiers may also exist in human populations. The reasons for these ethnic disparities remain unclear, but may reflect true genetic differences, environmental factors, including socio- economic, or a combination of factors. Individuals with angiotensinogen variants, i.e. MM genotype associated with decreased angiotensinogen levels were reported to have increased rates of hymenoptera venom allergy and more severe reactions during venom immunotherapy164. Similarly, among patients with tree nut and peanut allergy, lower serum ACE. levels were associated with more severe pharyngeal edema, presumably through decreased bradykinin metabolism [122-129].

The Observations that Beta-Adrenergic Blockade

Can exacerbate systemic anaphylaxis in rat and mouse models and in humans with severe anaphylaxis due to multiple causes, particularly when combined with angiotensin-converting enzyme (ACE) inhibitors, support a role for vasopressors. endogenous. in limiting the severity of pathophysiological changes in anaphylaxis. Degranulation of mast cells releases chymase, which can convert angiotensin I to angiotensin II, and thus may directly contribute to the increase in angiotensin II levels seen after anaphylaxis [130-134].

Although we do not know whether human IgE can also increase resistance to venoms (and we imagine we would have some difficulty enrolling volunteers for such a study), it is tempting to speculate that anaphylaxis induced by small amounts of venom (eg a single or wasp sting) represents only the most extreme and maladaptive end of a spectrum of acquired IgE-mediated immune responses to venom that includes, at the other end of the spectrum, properly regulated immune responses that can increase resistance to such poisons. The role of sex hormones in anaphylaxis is unclear. Anaphylaxis occurs more frequently in females than in males. However, analysis of patients in an anaphylaxis registry revealed an increased severity of anaphylaxis in male versus female patients aged 13–56 years, but no gender differences in anaphylaxis severity for prepubescent individuals or those older than 56 years.

Injectable Epinephrine

Is universally accepted as first-line therapy for anaphylaxis 10-12, and can counteract many of the pathophysiological changes in anaphylaxis by acting through: -alpha-1 adrenergic receptors to induce vasoconstriction, which prevents or reduces tissue edema/ airways, hypotension and distribution. friend; beta-1 adrenergic receptors to increase heart rate and cardiac contractility; -beta-2 adrenergic receptors to dilate the airways.

In addition, the action of epinephrine on beta-2 adrenergic receptors can potentially block further release of mediators (histamine and eicosanoids) from mast cells and possibly other effector cells.

Management and Treatment

An anaphylactic reaction should be treated immediately with an injection of epinephrine (adrenaline). The doses, available by prescription, come in an auto-injector that must be carried with you at all times. Two injections may be necessary to control symptoms. Here are some tips to reduce the risk of anaphylaxis know your trigger. If you have had anaphylaxis, it is very important to know what caused the reaction. An allergist can review your medical history and, if necessary, perform diagnostic tests. The most common causes are:

Food

Including peanuts, tree nuts such as walnuts and pecans, fish, shellfish, cow's milk and eggs. Latex: found in disposable gloves, IV tubing, syringes, adhesive tapes, and catheters. Healthcare workers, children with spina bifida and genitourinary abnormalities, and people who work with natural latex are at higher risk for latex-induced anaphylaxis.

Medication

Including penicillin, aspirin and non-steroidal anti-inflammatory drugs such as ibuprofen and anesthesia.

Insectsting

Bees, wasps, wasps, yellow jackets and fire ants are most likely to cause anaphylaxis.

Avoid your trigger. Avoidance is the most effective way to prevent anaphylaxis. An allergist can work with you to develop specific avoidance measures tailored specifically to your age, activities, occupation, hobbies, home environment, and access to medical care. Here are some general avoidance techniques for common triggers:

Food allergies
Become a label detective and be sure to carefully review all food ingredient labels to detect potential allergens. When eating out, ask the restaurant how the food is prepared and what ingredients are used. If you have a child with a history of anaphylaxis, it is imperative to ensure that school personnel are informed of the child's condition and a treatment plan is provided, including the administration of epinephrine [135-140].

Medicines
Make sure all your doctors are aware of any reactions you've had to medications so they can prescribe safe alternatives and warn you about other medications you may need to avoid. If there are no alternative medications, you may be a candidate for desensitization, a treatment that introduces a small dose of the medication you're allergic to. As your body becomes more tolerant of the medication, the dose may be increased over time. While the treatment is effective, it is only temporary and must be repeated if the medication is needed again in the future.

Insect bites. To help prevent biting insects, avoid walking barefoot on the grass, drinking from open cans of soft drinks, wearing brightly colored clothing with floral patterns, sweet-smelling perfumes, hairspray and lotion during the active season of insects in late summer and early fall. An allergist may also offer a preventative treatment called venom immunotherapy (or venom allergy shots) for insect sting allergy. The treatment works by injecting gradually increasing doses of purified insect venom and has been shown to be 90% to 98% effective in preventing future allergic reactions to insect bites.

Prompt recognition of the signs and symptoms of anaphylaxis is critical.

If you suddenly come into contact with your trigger, you should immediately follow the emergency plan prescribed by your doctor, including self-administration of epinephrine. If there is any doubt about a reaction, it is generally best to administer epinephrine. Be sure to keep your epinephrine auto-injector up to date. If an expired auto-injector is the only one available in an emergency situation, administer it immediately. Teachers and other caregivers should be informed about children who are at risk of anaphylaxis and know what to do in case of an allergic emergency.

Seek treatment. If a severe reaction occurs and epinephrine is administered, you should be transported to the nearest emergency facility by ambulance for additional monitoring. [141-185].

Tell your family and friends. Family and friends should be aware of your condition, your triggers and know how to recognize anaphylactic symptoms. If you have epinephrine, tell them where you keep it and how to use it. Identification of clothing. Wear and/or wear identification or jewelry (bracelet or necklace) noting the condition and offending allergens. Visit to a specialist. Allergists are specially trained to help you get control of your symptoms, perform diagnostic tests, and review treatment options so you can live the life you want. Look for additional resources. Additional information on allergies and anaphylaxis is available on the ACAAI website or at Food Allergy Research and Education (FARE) at www.foodallergy.org.
Additionally, helpful information can be found on the website of the Food Allergy and Anaphylaxis Association Team (FAACT) www.FoodAllergyAwareness.org.insect bites.

Treatment
Epinephrine. Dosage for adults:
0.3-0.5 mg intramuscularly i/m or s/c

Epinephrine. Children's dose depends on weight:
0.10 mg (for children 16.5 to 33 pounds-30 kg) - AUVI-Q brand only (pocketable and auto-injector).

0.15 mg (for children under 66 pounds)
0.3 mg (for children and adults over 66 pounds)

A second dose of epinephrine may be given as needed, but each dose requires careful monitoring. Once treated with epinephrine, subsequent care focuses on treating symptoms. Additional care may include:

- Supplemental oxygen, Intubation and Respiration with a mechanical ventilator
- Intravenous fluids and medications (such as antihistamines and cortisone to help with inflammation)
- Albuterol and/or Salbutamol (as a beta2- adrenergic to help with wheezing or other respiratory symptoms)
- Antihistamines - Benadryl (diphenhydramine) or Cetirizine, require up to 30 minutes to have an effect, so Epinephrine is the most advisable to give immediately.
- Promethazine should not be used in Anaphylactic Shock because it can worsen Hypotension and cause muscle necrosis.

Special Instructions
The necessary equipment includes:

- Epinephrine (adrenaline) ampoules 1:1000 (or epinephrine auto-injectors)
- Oral diphenhydramine (Benadryl) (12.5 mg/5 mL suspension) and 25 or 50 mg capsules or tables Salbutamol aerosol, 4 TB syringes
- (2) 3cc syringes (with/needle-22-25ga, length 1-1.5”)
- Tampons with alcohol
- Blood pressure cuff and stethoscope
- CPR mask

Doses of Epinephrine
Epinephrine (Adrenaline Chloride) 1:1000

- 0.1cc for children < 20 lbs. (0-12 months of age) from 9 kg -20.5 kg.
- 0.2cc for children 20 – 45 lbs. (1-4 years old)
- 0.3cc for children > 45 lbs. (> 4 years of age)
- 0.3cc for adults

Epinephrine Autoinjector Dosage Guidelines
0.15 mg (junior dose) indicated for children under 66 pounds < 30 kg

0.3 mg (adult dose) indicated for over 66 pounds - 30 kg > (EpiPen, Auvi-Q (epinephrine) dosing, indications, interactions, adverse effects, and more (medscape.com).

Treatment of Refractory Anaphylaxis

The RCUK (Resuscitation UK) 2021 guideline contains a specific algorithm for the treatment of refractory anaphylaxis. There is no set definition for refractory anaphylaxis, so the RCUK has defined it as 'anaphylaxis requiring ongoing treatment (due to persistent symptoms respiratory or cardiovascular) despite two appropriate doses of IM adrenaline.

A systematic review and meta-analysis found. about 3.4% of reactions treated with adrenaline have a suboptimal response to two doses of adrenaline, although most respond to three doses14. Early recognition is vital and early critical care support should be sought. The pathophysiology of refractory anaphylaxis is likely the result of persistent release of inflammatory mediators, insufficient circulating adrenaline (usually due to suboptimal dosing, reduced circulating blood volume, or, less commonly, tachyphylaxis 38. Equal plasma extravasation to one-third of the circulating blood volume can occur within minutes in severe reactions, and venous return can be impaired even in those without clinically apparent hemodynamic compromise.

The main goal in the treatment of refractory anaphylaxis is to optimize the delivery of adrenaline. Therefore, intravenous fluid infusion is essential to treat shock and ensure sufficient circulating volume to maintain cardiac output and deliver adrenaline at the tissue level. In cases where the ABC features of anaphylaxis persist despite two doses of IM adrenaline, a low-dose adrenaline. infusion is likely to be much more effective than IM or IV boluses 46-48 As such, this along with fluid resuscitation forms the basis of treatment in the 2021 guideline.

The risk of adverse effects due to i/v adrenaline is much higher than with IM administration. Excessive doses can lead to tachyarrhythmias, severe hypotension, myocardial infarction, stroke, and death. Therefore, i/v adrenaline should only be used by physicians experienced in the use and titration of vasopressors in their normal practice, and in a very closely monitored setting (including electrocardiography and blood pressure).

In cases of severe bronchospasm, an adrenaline infusion remains the cornerstone of treatment, but can be supplemented with nebulized and i/v bronchodilators. Magnesium is not recommended intravenously because of the risk of significant vasodilation. In critical upper airway obstruction, nebulized adrenaline may be helpful but should not take precedence over tracheal intubation.

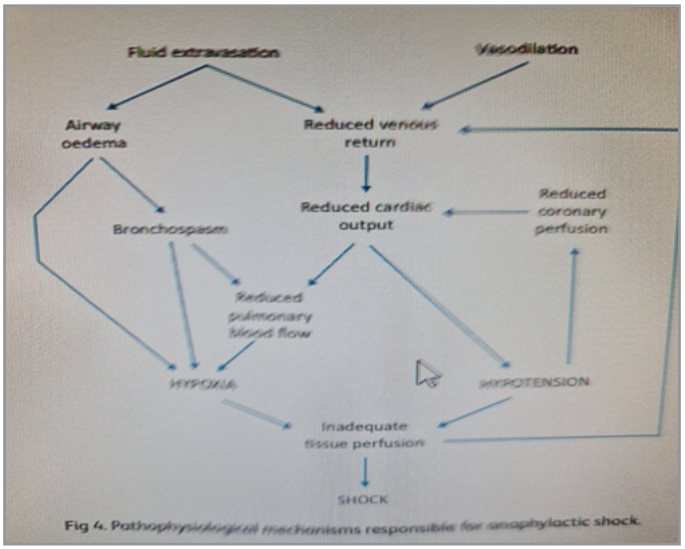
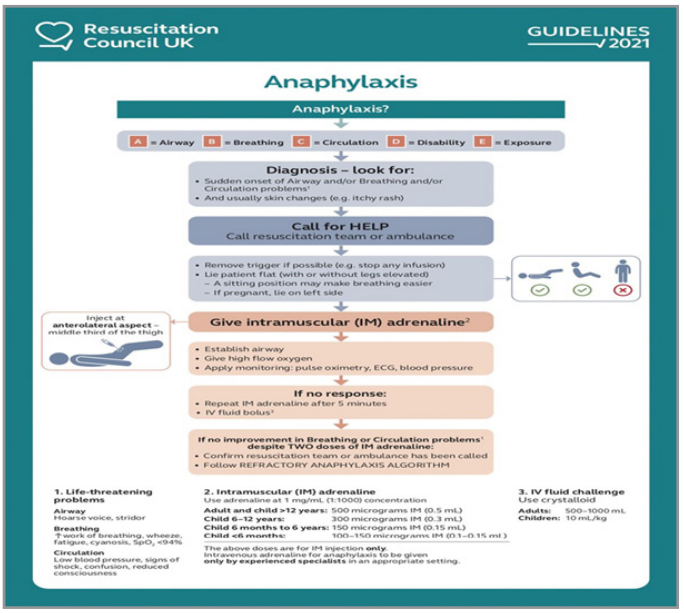


Fig 4. Pathophysiological mechanisms responsible for anaphylactic shock.

Phys-Pathology of Anaphylactic Shock, as a Type of Distributive Shock



One of the Anaphylaxis Treatment Algorithms

Conclusions

It is not known exactly the severe allergic reactions that have occurred in Albania, but it is necessary to equip the Health Centers because Anaphylaxis is an acute, life-threatening hypersensitivity disorder, defined as a generalized multi-systemic allergic reaction, with rapid development. Anaphylactic reactions were classified as IgE-mediated reactions, while anaphylactoid reactions as IgE-independent events.

The best way to avoid anaphylaxis is to the most important management strategy is avoidance of all - known triggers (allergens) -if the person has a food allergy, always read food labels and disclose your allergy when eating out (this means letting the staff know about your allergy).

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